Section V.
NEUROFIBROMATOSIS RESEARCH PROGRAM

CONTENTS

CDMRP

Neurofibromatosis Research Program

Vision: Decrease the impact of neurofibromatosis.

Mission: To promote research directed toward the understanding, diagnosis, and treatment of NF1 and NF2 and to enhance the quality of life for individuals with the disease.

Congressional Appropriations for Peer Reviewed Research
$37.3M in FY96–99, $15M in FY00, and $17M in FY01

Award Summary
45 awards from the FY96–99 appropriations
20 awards from the FY00 appropriation
~20 awards anticipated from the FY01 appropriation

The Disease

"The U.S. Army NF program has become the single most important factor contributing to progress in research on NF in the world."

—Allan Rubenstein, M.D.
Director, Mount Sinai NF Research and Treatment Center
FY01 NFRP Integration Panel Chair

Neurofibromatosis (NF) includes two distinct genetic disorders of NF1 and NF2 genes adversely affecting the nervous system. NF1 results from mutations in the NF1 gene, which is located on chromosome 17 and codes for a complex protein known as neurofibromin. NF2 results from mutations in a tumor suppressor gene, which is located on chromosome 22 and codes for a protein known as merlin or schwannomin. Together, these two disorders affect more than 100,000 Americans of both genders and all ethnic groups. NF1 and NF2 are usually inherited as an autosomal dominant disorder. A parent with NF has a 50% chance of passing on the disorder to his/her child. However, 30 to 70% of NF1 and NF2 cases arise as a result of a spontaneous genetic change. These disorders usually result in tumors involving nerves anywhere in the body; however, non-nervous tissue such as bone and skin can also be affected. Tumors can cause disfigurement, deafness, blindness, bone deformation, learning disabilities, and, in some cases, death. The tumors that appear in NF patients can vary significantly, even among affected individuals in the same family. While surgical intervention can provide palliative relief, there is no cure at this time.

NF1 is the more common type, affecting about 1 in 4,000[1] individuals, and is also known as Von Recklinghausen's Disease or Peripheral NF. A common characteristic of NF1 is the appearance of flat, pigmented markings on the skin called café-au-lait spots. NF1 is also characterized by neurofibromas, which are growths that develop on or just under the skin and are composed of tissue from the nervous system and fibrous tissue. Symptoms of NF often appear at birth and usually by the age of 10. Approximately 50% of people with NF1 have learning disabilities.

[1] *Report on Neurofibromatosis*, Department of Health and Human Services, Public Health Service, National Institutes of Health, National Institute of Neurological Disorders and Stroke, 1993.

NF2 is rarer than NF1, only affecting about 1 in 40,000[1] individuals, and is also known as bilateral acoustic NF (BAN). NF2 is characterized by the growth of tumors on nerves of the inner ear, among other complications. The inner ear neuromas in NF2 patients cause hearing loss and can eventually result in deafness. Hearing loss in NF2 patients can appear in the teen years.

"I am honored to serve as the Program Manager for the DOD's Neurofibromatosis Research Program. A great personal accomplishment would be to play a role in decreasing the impact of this disease."

—Richard Kenyon, Ph.D.
NFRP Program Manager

History of the Neurofibromatosis Research Program

——Program Background

The Congressionally Directed Medical Research Programs (CDMRP) began managing the Department of Defense (DOD) Neurofibromatosis Research Program (NFRP) in response to the fiscal year 1996 (FY96) *Senate Appropriations Committee Report No. 104–124*, which provided $8 million (M) for research in NF.[2] At that time, the U.S. Army Medical Research and Materiel Command (USAMRMC) convened a meeting of expert scientists, clinicians, and consumer advocates in the field of NF to define the goals and areas of emphasis of the program. The overall mission of the NFRP has been, and continues to be, funding basic and clinical research relevant to NF that will result in substantial improvements in the understanding, diagnosis, and treatment of NF1 and NF2 and to enhance the quality of life for individuals with the disease.

——Congressional Appropriation and Funding History

From FY96–01, Congress appropriated a total of $69.3M to fund peer review NF research through the NFRP. The investment strategy focuses on the program's vision to decrease the impact of NF. A total of 65 awards have been made in the FY96–00 programs across the categories of research, infrastructure, and training/recruitment. The NFRP has developed a multidisciplinary research portfolio that encompasses basic, clinical, and population-based research projects. Appendix B, Table B–3, summarizes the congressional appropriations, and the investment strategy executed by the NFRP for FY00–01. Additional details of the FY96–99 programs appear in the *DOD CDMRP Annual Reports* of September 1999 and of September 2000.

[1] *Report on Neurofibromatosis*, Department of Health and Human Services, Public Health Service, National Institutes of Health, National Institute of Neurological Disorders and Stroke, 1993.

[2] The U. S. Army Medical Research and Materiel Command, but not the CDMRP, was also responsible for managing congressional appropriations in FY92 for NF research.

FY00 Program

Congress appropriated $15M in FY00 to continue the peer reviewed DOD NFRP. Support for training of NF researchers, encouragement of established scientists in the field, and attraction of new scientific expertise from other fields are all considered essential to the NF community. To address these essential items, the programmatic vision was implemented by offering four award mechanisms: Investigator-Initiated Research Awards (with the option for Nested Postdoctoral Traineeships), New Investigator Awards, Idea Awards, and Clinical Trial Awards. Table V–1 provides a summary of the FY00 NFRP award mechanisms in terms of dollars and number of awards.

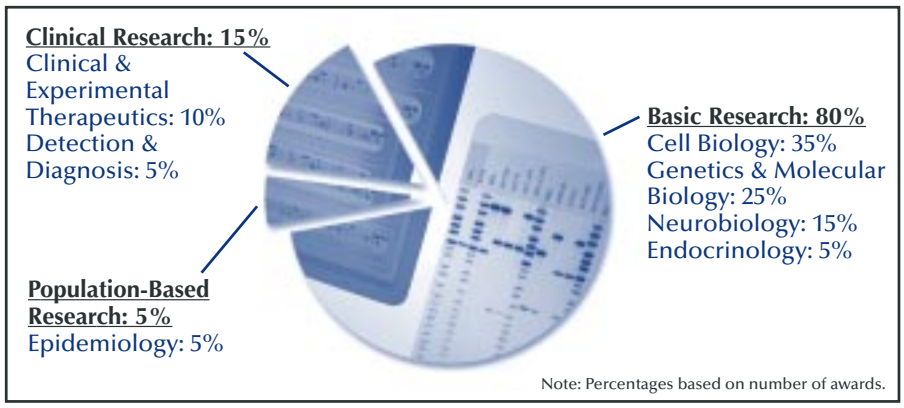


Figure V–1. FY00 NFRP Portfolio by Research Area

Investigator-Initiated Research Awards support experienced researchers. Including the awards made in FY00, the NFRP has made a total of 37 Investigator-Initiated Research Awards, through which 26 postdoctoral trainees have been supported. The New Investigator Awards made in FY00 support NF research by independent investigators early in their careers. Idea Awards support research that represents new paradigms in the study of NF, challenges existing paradigms,

"While the importance of the research efforts made possible by the U.S. Army NF program cannot be overstated, the program does something even more vital for all of us living with NF: It gives us hope. And with hope, we start planning our futures, rather than spending our lives bracing for the next crisis."

—Michie Stovall O'Day
National Neurofibromatosis Foundation
Consumer Peer Reviewer

Table V–1. Funding Summary for the FY00 NFRP

Award Mechanism	Number of Proposals Received	Number of Awards	Investment
Investigator-Initiated Research Awards	15	7	$7.5M
New Investigator Awards	11	6	$2.7M
Idea Awards	12	6	$1.9M
Clinical Trial Awards	3	1	$0.4M
Total	**41**	**20**	**$12.5M**

or examines a problem from a new perspective. Clinical Trial Awards are aimed at testing new agents for the treatment of NF. In FY00, the NFRP made its first award for a Clinical Trial for a Phase 2 study.

FY01 Program

Congress continued the DOD NFRP in FY01 with a $17M appropriation. The programmatic vision in FY01 called for Investigator-Initiated, New Investigator, Idea, and Clinical Trial Award mechanisms again, plus offered a new award mechanism, Therapeutic Development Awards. This new award is intended to boost the number of NF clinical trials by sponsoring the development and evaluation of preclinical model systems for NF1 and NF2. In response to the Program Announcement, 48 proposals were received in August 2001. Scientific peer review and programmatic review are scheduled for October and December 2001, respectively. Approximately 20 awards are anticipated.

A new feature of the FY01 NFRP was electronic proposal submission. The electronic format was well received by the research community and will ultimately result in reduced administrative costs. For more information on electronic proposal administration, see Section II of this report.

Scientific Achievements

The DOD NFRP-supported research is producing advances in basic NF research and bringing laboratory research into clinical trials. The success NFRP-funded research can be gauged, in part, by the number of resultant publications, abstracts/presentations, and patents/licensures reported by awardees. This information is summarized in Table V–2. The following projects represent some of the most exciting advances that are being supported by the NFRP.

Identifying a New Gene Associated with Early Onset of Skin Neurofibromas. Karen G. Stephens, Ph.D., University of Washington: Understanding the important changes in a genetic disorder, such as neurofibromatosis, requires detailed knowledge of not only the NF1 gene that is responsible for the disorder, but also of other genes that function to increase or decrease the severity. NFRP researchers at the University of Washington have discovered that when a deletion occurs that inactivates both the NF1 gene and another nearby unknown gene, it

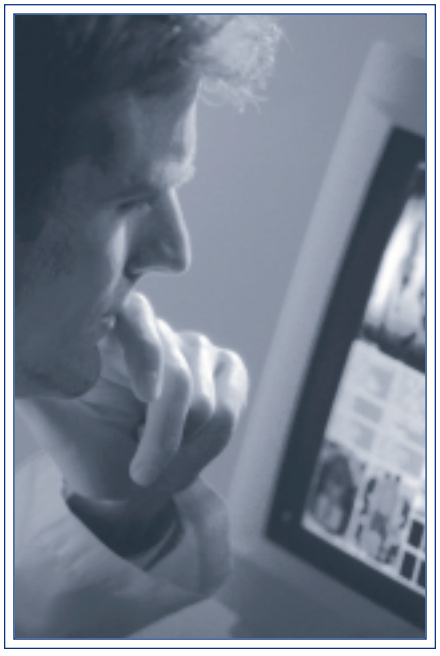
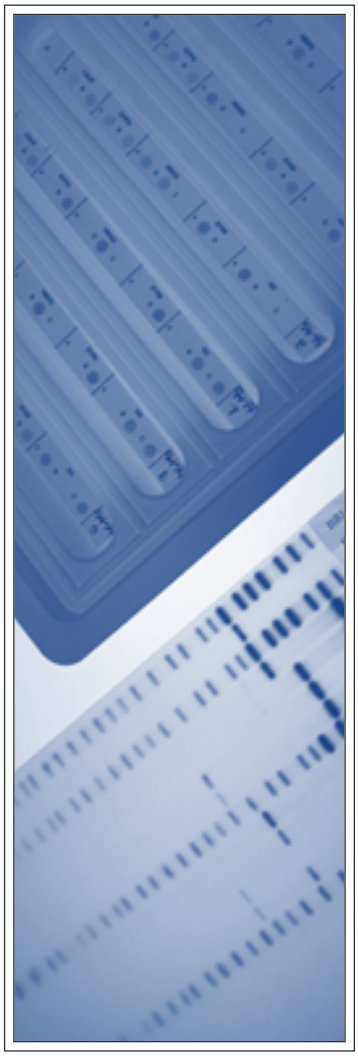


Table V–2. FY96–98 NFRP Award Outcomes

Number of Awards	24
Publications in Scientific Journals	>35
Abstracts/Presentations at Professional Meetings	>20
Patents/Licensures (including applications)	>6

Bringing Therapeutic Agents to Patients

There are presently only a small number of clinical trials of drugs to treat NF. The NFRP hopes to change this using a multifaceted approach. First, the NFRP is building an infrastructure to support the development of future clinical trials by offering Natural History/Consortia Awards. The goal of these awards is to establish large, multidisciplinary consortia of clinical centers to generate quantitative data on tumor growth rates that can be readily translated into clinical trials for NF. Second, the NFRP is encouraging the development and evaluation of preclinical model systems for NF by offering Therapeutic Development Awards. Third, the NFRP is supporting Phase 1, Pilot, and Phase 2 clinical drug trials. The NFRP hopes that this comprehensive approach will greatly accelerate the progression of therapeutic agents and procedures from bench to bedside. ✦



causes skin tumors (neurofibromas) to appear much earlier in life and in greater numbers. The researchers have identified a novel mechanism for how the deletion occurs and a specific chromosomal site where it occurs. These findings have identified specific genetic mechanisms that can cause neurofibromatosis and narrowed the region of the chromosome in which to search for the new unknown gene that enhances tumor formation. Identification of a tumor enhancer gene and understanding how it functions will increase our understanding of how neurofibromas develop and may ultimately allow for the development of new therapeutic strategies that slow or halt neurofibroma growth.

Finding a Protein That Interacts with the NF2 Tumor Suppressor Protein Schwannomin. Stefan-M. Pulst, M.D., Cedars-Sinai Medical Center: The NF2 gene encodes a protein termed schwannomin (also known as merlin), which suppresses cell growth. When the NF2 gene is mutated, lack of schwannomin production leads to the uncontrolled cell growth that is characteristic of tumor formation. NFRP-funded researchers at the Cedars Sinai Medical Center have identified several proteins that have been shown to interact with schwannomin. One of these proteins is hepatocyte growth factor (HGF)-regulated tyrosine kinase substrate (HRS). HGF is known to act as a stimulator of cell growth and movement. HRS binds specifically to schwannomin when the protein is in its "open" conformation. Mutated schwannomin molecules lose the ability to bind HRS. They also found that overexpression of HRS or schwannomin in cells altered similar cellular processes (e.g., reduced cell growth, decreased cell movement, and abnormalities in cell spreading). Schwannomin and HRS collocalize at endosomes, suggesting that both may be involved in trafficking of molecules from the cell membrane.

Imaging the Brains of Children and Young Adults with NF1. Laurie E. Cutting, Ph.D., Kennedy Krieger Institute: NF1 patients frequently suffer from a condition called megalencephaly, which involves an abnormally large brain. Megalencephaly has been associated with selective cognitive impairment, among other abnormalities. NFRP-funded researchers at the Kennedy Krieger Institute are characterizing megalencephaly in NF1 patients using magnetic resonance

imaging and three-dimensional volumetric radiofrequency spoiled gradient magnetic resonance imaging scans. They have recruited 18 males with NF1, and 18 age-matched controls, ranging from 5 to 24 years of age. Seven of the 18 males with NF1 were diagnosed with attention deficit hyperactivity disorder (ADHD). The researchers found that, as compared to controls, males with NF-1 without ADHD were megalencephalic, while males with NF-1 with ADHD were not megalencephalic. However, all males with NF-1 had an increased volume of white matter (i.e. areas of brain containing nerve cell fibers) in specific brain regions, regardless of ADHD status. They also determined that NF1 patients with ADHD had a decreased volume of gray matter (i.e. areas of brain containing nerve cell bodies) in one brain region compared to NF1 patients without ADHD or controls. The researchers plan to further elucidate the nature and functional ramification of white and gray matter abnormalities in NF1 using multiple magnetic resonance modalities and comprehensive neuroimaging-behavioral correlations.

Elucidating the Normal Functions of the Nf1 Gene. Nancy Ratner, Ph.D., University of Cincinnati: NF1 patients develop neurofibromas, which are benign tumors associated with nerves that run throughout the body. Neurofibromas are composed of supporting cells called Schwann cells and collagen-producing cells called fibroblasts; fibroblast-derived collagen accounts for much of the bulk of neurofibromas. The mechanisms underlying the development of these tumors have yet to be fully elucidated. NFRP-funded researchers at the University of Cincinnati are elucidating roles played by the *Nf1* gene in the development of neurofibromas in mice. They used mice with one normal *Nf1* gene and one defective *Nf1* gene. These animals do not usually develop neurofibromas. The researchers tested these mice in a well-characterized skin wound-healing model. They found that wounding *Nf1*-defective fibroblasts (but not fibroblasts with normal *Nf1* genes) could lead to the development of extensive collagen-rich matrix. In addition, they found that *Nf1*-defective fibroblasts exhibited abnormalities similar to those observed in human neurofibromas. Overall, the researchers are showing that *Nf1* is a key regulator of fibroblast responses to injury. While basic research studies such as this one may not directly benefit NF patients, they provide information that is critical for the development of future clinical trials and therapeutics.

"The NFRP has formed a partnership that allows the participants to more fully recognize and appreciate the commitment that the Army, researchers, professionals, and consumers have in finding treatments for those who have neurofibromatosis, including my children and husband."

—Brenda Duffy
President, Neurofibromatosis, Inc.
Integration Panel Member

Partnerships to Study NF

With their NFRP-funded awards, investigators at the Massachusetts Institute of Technology and the University of California San Francisco have been asked to join the Mouse Models of Human Cancers Consortium (MMHCC) sponsored by the National Cancer Institute (NCI). The MMHCC was established in 1999 to support the formation of consortia to develop and validate mouse models of cancer. NFRP awardees are the first investigators with an NF mouse model to join the consortium. All of these models are being used to test new approaches to detection, diagnosis, and imaging, and to evaluate prevention and treatment of various diseases including NF. Through combined efforts and sharing of valuable information, NFRP-funded and NCI-funded researchers will be able to more efficiently achieve their common goals. ✦

"After identification of the NF2 gene, it has been very difficult to define the function of schwannomin, the protein encoded by the NF2 gene. Support from the NFRP has allowed us to search for proteins that interact with schwannomin, thus identifying novel pathways important in the pathogenesis of NF2 tumors."

—Stefan-M. Pulst, M.D.
Carmen and Louis Warschaw Chair
Cedars-Sinai Medical Center
NFRP Award Recipient

Creating a Unique Mouse Model of a Common Brain Tumor. Tyler Jacks, Ph.D., Massachusetts Institute of Technology: Astrocytomas are highly infiltrative, malignant brain tumors made up of star-shaped cells called astrocytes. They are the leading cause of brain cancer in humans and are observed at increased frequency in NF1 patients compared to the general population. Current mouse models of astrocytomas are based on the overexpression of genes that cause tumors to form. These models have not been very successful due to limited tumor progression and low tumor penetrance into surrounding tissue. NFRP-funded researchers at the Massachusetts Institute of Technology have created the first reported mouse model of astrocytoma based on the loss of genes that normally suppress tumor formation. The genes knocked out in this model are *Nf1* and *Trp53*. This model exhibits a wide range of astrocytoma stages, from the relatively mild, low-grade astrocytoma to the extremely malignant glioblastoma multiforme. While the loss of *Nf1* in mice does not lead to the formation of tumors that are observed in NF1 patients, the combined loss of *Nf1* and *Trp53* results in the development of astrocytomas in the central nervous system and malignant tumors surrounding nerves in the peripheral nervous system. Therefore, loss of *Trp53* function appears to be critical for the formation of malignant tumors in this model. Overall, this promising model can be used to dissect tumor progression and test potential therapeutics.

Summary

Since 1996, the DOD NFRP has been responsible for managing $69.3M in congressional appropriations, which has resulted in 65 awards for FY96–00. These awards have made important contributions to understanding the molecular mechanisms, natural history, and treatment of NF1 and NF2. The NFRP has developed a multidisciplinary portfolio that encompasses basic, clinical, and population-based research projects. Projects funded by the NFRP are yielding results that will improve the understanding, diagnosis, and treatment of NF1 and NF2 as well as enhance the quality of life for individuals with this disease.

FY01 Integration Panel Members

***Chair*, Allan Rubenstein, M.D.:** Director, Mount Sinai Neurofibromatosis Research and Treatment Center, Department of Neurology at Mount Sinai Hospital. Medical Director, the New York Neurofibromatosis Institute. Helped co-found National Neurofibromatosis Foundation, Inc., and currently serves as its Medical Director.

***Chair-Elect*, Peter Bellermann:** Consumer; President, National Neurofibromatosis Foundation, Inc. Chair, International Neurofibromatosis Association. Advisor to the World Health Organization on ethical, social, economic, and political issues in genetics.

***Chair Emeritus*, David Pleasure, M.D.:** Professor of Neurology, Pediatrics, and Orthopaedic Surgery at the University of Pennsylvania. Director of the Joseph Stokes, Jr., Research Institute at Children's Hospital of Philadelphia.

Peter Adamson, M.D.: Chief, Division of Clinical Pharmacology and Therapeutics at the Children's Hospital of Philadelphia. Associate Professor of Pediatrics at the University of Pennsylvania School of Medicine.

Neal Copeland, Ph.D.: Director of the Mouse Cancer Genetics Program at the National Cancer Institute, Frederick Cancer Research and Development Center.

Brenda Duffy, M.A.: Consumer; President, Neurofibromatosis, Inc.

Kurt Fischbeck, M.D.: Chief, Neurogenetics Branch at the National Institute of Neurological Disorders and Stroke, National Institutes of Health.

Zach Hall, Ph.D.: Executive Vice-Chancellor of Research at the University of California, San Francisco.

John Mulvihill, M.D.: Kimberly V. Talley Chair of Genetics, Professor of Pediatrics, Director of the Program in Human Genetics, and Professor of Biostatistics and Epidemiology at the University of Oklahoma Health Sciences Center.

Robert Murray, Jr., M.D., Ph.D.: Professor and Chair, Graduate Department of Genetics and Human Genetics at Howard University. Professor of Pediatrics and Medicine, and Chief of the Division of Medical Genetics, Department of Pediatrics and Child Health in the College of Medicine at Howard University. Member of National Academy of Sciences' Institute of Medicine.

Louis-Gilbert Vézina, M.D.: Director of Neuroradiology in the Department of Diagnostic Imaging and Radiology at Children's National Medical Center in Washington, DC. Associate Professor of Radiology and Pediatrics at George Washington University.

For more information about the NFRP and other programs managed by the CDMRP, visit **http://cdmrp.army.mil**